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NEWS 2 MAY 01 New CAS web site launched  
NEWS 3 MAY 08 CA/CAPplus Indian patent publication number format defined  
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NEWS 5 MAY 21 BIOSIS reloaded and enhanced with archival data  
NEWS 6 MAY 21 TOXCENTER enhanced with BIOSIS reload  
NEWS 7 MAY 21 CA/CAPplus enhanced with additional kind codes for German patents  
NEWS 8 MAY 22 CA/CAPplus enhanced with IPC reclassification in Japanese patents  
NEWS 9 JUN 27 CA/CAPplus enhanced with pre-1967 CAS Registry Numbers  
NEWS 10 JUN 29 STN Viewer now available  
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NEWS 12 JUL 02 LEMBASE coverage updated  
NEWS 13 JUL 02 LMEDLINE coverage updated  
NEWS 14 JUL 02 SCISEARCH enhanced with complete author names  
NEWS 15 JUL 02 CHEMCATS accession numbers revised  
NEWS 16 JUL 02 CA/CAPplus enhanced with utility model patents from China  
NEWS 17 JUL 16 CAPplus enhanced with French and German abstracts  
NEWS 18 JUL 18 CA/CAPplus patent coverage enhanced  
NEWS 19 JUL 26 USPATFULL/USPAT2 enhanced with IPC reclassification  
NEWS 20 JUL 30 USGENE now available on STN  
NEWS 21 AUG 06 CAS REGISTRY enhanced with new experimental property tags  
NEWS 22 AUG 06 BEILSTEIN updated with new compounds  
NEWS 23 AUG 06 FSTA enhanced with new thesaurus edition  
NEWS 24 AUG 13 CA/CAPplus enhanced with additional kind codes for granted patents  
NEWS 25 AUG 20 CA/CAPplus enhanced with CAS indexing in pre-1907 records

NEWS EXPRESS 29 JUNE 2007: CURRENT WINDOWS VERSION IS V8.2,  
CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),  
AND CURRENT DISCOVER FILE IS DATED 05 JULY 2007.

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FILE 'HOME' ENTERED AT 11:29:14 ON 20 AUG 2007

=> file medline, biosis, wpids  
COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
0.21	0.21

FULL ESTIMATED COST

FILE 'MEDLINE' ENTERED AT 11:29:31 ON 20 AUG 2007

FILE 'BIOSIS' ENTERED AT 11:29:31 ON 20 AUG 2007  
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FILE 'WPIDS' ENTERED AT 11:29:31 ON 20 AUG 2007  
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=> (toll-like receptor 8)  
(TOLL-LIKE IS NOT A RECOGNIZED COMMAND  
The previous command name entered was not recognized by the system.  
For a list of commands available to you in the current file, enter  
"HELP COMMANDS" at an arrow prompt (=>).

=> s (TLR-8)  
L1 76 (TLR-8)

=> s l1 and (Toll-like receptor-8)  
L2 50 L1 AND (TOLL-LIKE RECEPTOR-8)

=> s l2 and (2-aminopyridine)  
L3 0 L2 AND (2-AMINOPYRIDINE)

=> s l2 and (imidazoquinoline)  
L4 5 L2 AND (IMIDAZOQUINOLINE)

=> d l4 ti abs ibib tot

L4 ANSWER 1 OF 5 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN  
TI The antitumoral mode of action of imiquimod and other imidazoquinolines.  
AB Imiquimod, the lead compound of the imidazoquinoline family of nucleoside analogues, has shown good efficacy against a variety of tumors of different origin. The mode of action of imiquimod and related compounds, which we have begun to understand in some detail in recent years, is complex and interesting inasmuch as it appears to comprise several presumably mutually enhancing components. Predominant amongst its actions is the induction of pro-inflammatory cytokines through agonistic activity towards Toll-like receptor (TLR)-7 and TLR-8, and consecutively, activation of the central transcription factor NF-kappa B. This activity stimulates the production of pro-inflammatory cytokines, chemokines and other mediators resulting in activation of antigen-presenting cells and the mounting of a profound Th1-weighted antitumoral cellular immune response. In addition, there are a number of secondary effects on the molecular and cellular level that can be explained through the activation of NF-kappa B. The pro-inflammatory activity of imiquimod appears to be augmented by suppression of a negative regulatory feedback mechanism which normally limits inflammatory responses. This is achieved independent of TLR-7 and TLR-8 through interference with adenosine receptor signaling pathways, particularly the A(2A) subtype, and receptor-independent reduction of adenylyl cyclase activity. Finally, at higher, albeit therapeutically relevant concentrations, imiquimod exerts a pro-apoptotic activity against tumor cells. Induction of apoptosis by imiquimod appears to be dependent on Bcl-2 proteins and involves caspase activation. The combination of multiple, presumably synergistic anti-tumoral functions by a single compound represents an interesting principle of pathogenesis-oriented,

anti-neoplastic therapy.

ACCESSION NUMBER: 2007:215335 BIOSIS  
DOCUMENT NUMBER: PREV200700214472  
TITLE: The antitumoral mode of action of imiquimod and other  
imidazoquinolines.  
AUTHOR(S): Schoen, Margarete; Schoen, Michael P. [Reprint Author]  
CORPORATE SOURCE: Univ Wurzburg, Rudolf Virchow Ctr, DFG Res Ctr Expt Biomed,  
Versbacher Str 9, D-97078 Wurzburg, Germany  
michael.schoen@virchow.uni-wuerzburg.de  
SOURCE: Current Medicinal Chemistry, (2007) Vol. 14, No. 6, pp.  
681-687.  
ISSN: 0929-8673.  
DOCUMENT TYPE: Article  
LANGUAGE: English  
ENTRY DATE: Entered STN: 28 Mar 2007  
Last Updated on STN: 28 Mar 2007

L4 ANSWER 2 OF 5 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN  
TI The small antitumoral immune response modifier imiquimod interacts with  
adenosine receptor signaling in a TLR7-and TLR8-independent fashion.  
AB Imiquimod, a small-molecule immune response modifier of the  
imidazoquinoline family, has shown profound antitumoral and  
antiviral efficacy both in vitro and in clinical applications in vivo. It  
has been demonstrated that this activity is mediated through the Toll-like  
receptor (TLR)7- and TLR8-signaling cascade resulting in the secretion of  
proinflammatory cytokines and, consecutively, induction of a  
tumor-directed cellular immune response. In addition, imiquimod exerts a  
direct proapoptotic activity in tumor cells. We demonstrate here that  
imiquimod induces activation of the transcription factor NF-kappa B and  
the downstream production of proinflammatory cytokines in the absence of  
TLR7 and TLR8. In Chinese hamster ovary cells stably transfected with the  
human adenosine receptor subtypes, we then show in radioligand-binding  
competition experiments that imiquimod binds to adenosine receptors at  
concentrations relevant in clinical settings, with highest affinities to  
the A(1) and A(2A) subtypes. The effect on the receptor-mediated  
activation of adenylyl cyclase was also studied, and these experiments  
revealed that imiquimod acts as an adenosine receptor antagonist. In  
addition, imiquimod had an inhibitory effect on adenylyl cyclase activity  
downstream from the receptor. Finally, using transformed human  
keratinocytes, we provide experimental evidence that imiquimod and A2A  
adenosine receptor-specific compounds similarly induce proinflammatory  
cytokines in the absence of immune cells. Thus, imiquimod appears to  
suppress an important feedback mechanism of inflammation by antagonism of  
adenosine receptor-dependent increase of cAMP and a concomitant  
receptor-independent inhibition of cAMP production. These novel  
mechanisms presumably act synergistic with the positive induction of  
proinflammatory cytokines and can, at least in part, explain the profound  
inflammation observed in some patients in vivo.

ACCESSION NUMBER: 2006:603217 BIOSIS  
DOCUMENT NUMBER: PREV200600613866  
TITLE: The small antitumoral immune response modifier imiquimod  
interacts with adenosine receptor signaling in a TLR7-and  
TLR8-independent fashion.  
AUTHOR(S): Schoen, Michael P. [Reprint Author]; Schoen, Margarete;  
Klotz, Karl-Norbert  
CORPORATE SOURCE: Univ Wurzburg, Rudolf Virchow Ctr, DFG Res Ctr Expt Biomed,  
Versbacher Str 9, D-97078 Wurzburg, Germany  
michael.schoen@virchow.uni-wuerzburg.de  
SOURCE: Journal of Investigative Dermatology, (JUN 2006) Vol. 126,  
No. 6, pp. 1338-1347.  
CODEN: JIDEAE. ISSN: 0022-202X.  
DOCUMENT TYPE: Article  
LANGUAGE: English  
ENTRY DATE: Entered STN: 15 Nov 2006

L4 ANSWER 3 OF 5 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN  
TI Polymorphisms in TLR7 and 8 affect severity of hepatic fibrosis and  
inflammation in individuals infected with the hepatitis C virus from a  
single source.  
AB Background and Aims: Toll-like receptors (TLRs) are type I transmembrane  
proteins, which are highly conserved through evolution. They activate  
innate immunity by recognizing and binding to a wide variety of  
pathogenic substances. TLR7 and 8 both respond to the synthetic  
imidazoquinoline compounds, known to have anti-viral properties.  
TLR7 and probably TLR8 have also been demonstrated to recognize single  
stranded viral RNA. This study aimed to assess the involvement of  
inherited variations in TLR7 and 8 in determining disease outcome in HCV  
infected individuals. Methods: 223 women all exposed to HCV genotype 1b  
from a single donor, and including 85 who had spontaneously cleared the  
virus and 138 chronically infected, were genotyped for TLR 7 and 8  
polymorphisms and haplotype tagging was performed. The frequencies of  
these polymorphisms were then compared with disease activity and severity.  
Results: TLR 7 and 8 genotypes were compared with HCV PCR status, ALT  
levels and liver histology. There was no association between HCV PCR  
status and the TLR polymorphisms. Of the 5 SNPs examined in TLR8, wild  
types were associated with significantly worse fibrosis for 2 SNP loci  
(TLR8C (C401T); 1.38 vs 0.78,  $p = 0.03$ , TLR8D (C426T); 1.39 vs. 0.70,  $p =$   
0.018). Degree of inflammation was worse in TLR8B (A796C) wild type; 5.1  
vs. 4.2,  $p = 0.008$ , and this group also had higher ALT levels; 66 vs. 41,  
 $p = 0.018$ . TLR7B (C149T) was associated with lower inflammation and 4.4  
vs. 5.7,  $p = 0.015$  ALT levels; 47.8 vs. 73.4,  $p = 0.014$ . On analysis of  
haplotypes, those containing the minor allele for TLR8A or TLR8B had  
significantly less fibrosis ( $p = 0.025$ ,  $p < 0.01$ , respectively).  
Haplotypes containing the minor allele for TLR7B had significantly lower  
inflammatory scores,  $p < 0.025$ . No haplotype was associated with viral  
clearance. Conclusion: Consistent with prior functional data regarding  
viral clearance, HCV viral clearance was not associated with any of the  
TLR 7 or 8 SNPs examined in this study. However, SNPs in TLR 7 and 8 were  
associated with a lesser degree of hepatic inflammation and fibrosis.  
Further functional characterisation of these SNPs could provide important  
information on the response of the host to HCV infection.

ACCESSION NUMBER: 2006:499496 BIOSIS  
DOCUMENT NUMBER: PREV200600505816  
TITLE: Polymorphisms in TLR7 and 8 affect severity of hepatic  
fibrosis and inflammation in individuals infected with the  
hepatitis C virus from a single source.  
AUTHOR(S): Goulding, Carol A.; Mc Manus, Ross; Murphy, Anne; Mac  
Donald, George S.; Dring, Megan; Hegarty, John; Kiernan,  
Susan Me; Kelleher, Dermot  
SOURCE: Gastroenterology, (APR 2006) Vol. 130, No. 4, Suppl. 2, pp.  
A780.  
Meeting Info.: Digestive Disease Week Meeting/107th Annual  
Meeting of the American-Gastroenterological-Association.  
Los Angeles, CA, USA. May 19 -24, 2006. Amer Gastroenterol  
Assoc Inst.  
CODEN: GASTAB. ISSN: 0016-5085.  
DOCUMENT TYPE: Conference; (Meeting)  
Conference; (Meeting Poster)  
LANGUAGE: English  
ENTRY DATE: Entered STN: 4 Oct 2006  
Last Updated on STN: 4 Oct 2006

L4 ANSWER 4 OF 5 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN  
TI Immune modulation and apoptosis induction: Two sides of the antitumoral  
activity of imiquimod.  
AB Imiquimod, the first member of the imidazoquinoline family of  
immune response modifiers, has proven good clinical efficacy against basal

cell carcinomas and actinic keratoses in several independent studies. In addition, there is recent evidence that imiquimod is also efficacious against other tumors such as cutaneous metastases of malignant melanoma or vascular tumors. Imiquimod exerts its antitumoral effect, at least in part, through binding to TLR-7 and TLR-8 on dendritic cells followed by secretion of a multitude of proinflammatory cytokines. The net result of this proinflammatory activity is a profound tumor-directed cellular immune response. However, recent experimental and clinical data indicate that imiquimod also possesses considerable direct proapoptotic activity against tumor cells both in vitro and in vivo. This novel mode of action appears to be independent of membrane bound death receptors, but involves caspase activation. Induction of apoptosis by imiquimod is, at least in part, presumably mediated through Bcl-2-dependent release of mitochondrial cytochrome c and subsequent activation of caspase-9. The structural analogue, resiquimod, exhibited very limited, if any, such proapoptotic activity, possibly due to its lacking ability to enter the cell. Bypassing molecular mechanisms of apoptosis deficiency by a topical compound may be of great utility for treating certain cutaneous tumors.

ACCESSION NUMBER: 2004:282528 BIOSIS  
DOCUMENT NUMBER: PREV200400282627  
TITLE: Immune modulation and apoptosis induction: Two sides of the antitumoral activity of imiquimod.  
AUTHOR(S): Schoen, M. P. [Reprint Author]; Schoen, M.  
CORPORATE SOURCE: Rudolf Virchow CtrDFG Res Ctr Expt Biomed, Univ Wurzburg, Versbacher Str 9, D-97078, Wurzburg, Germany michael.schoen@virchow.uni-wuerzburg.de  
SOURCE: Apoptosis, (May 2004) Vol. 9, No. 3, pp. 291-298. print. ISSN: 1360-8185 (ISSN print).  
DOCUMENT TYPE: Article  
General Review; (Literature Review)  
LANGUAGE: English  
ENTRY DATE: Entered STN: 9 Jun 2004  
Last Updated on STN: 9 Jun 2004

L4 ANSWER 5 OF 5 WPIDS COPYRIGHT 2007 THE THOMSON CORP on STN

TI Immunostimulatory combination for inducing toll like receptor 8-mediated biological activity e.g. synthesis of cytokine for treating e.g. cancer comprises toll like receptor 8 agonist in combination with immunostimulatory oligonucleotide

AN 2006-424284 [43] WPIDS

AB WO 2006063152 A2 UPAB: 20060706

NOVELTY - An immunostimulatory combination (C1) comprises a toll like receptor (TLR)8 agonist in combination with an immunostimulatory oligonucleotide to induce at least one TLR8-mediated biological activity.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for inducing TLR8-mediated biological activity in immune cells, involving contacting the immune cells with (C1) to increase a TLR8-mediated biological activity of the cells to a greater extent than contacting the immune cells with the TLR8 agonist without the immunostimulatory oligonucleotide.

ACTIVITY - Immunostimulant; Cytostatic; Antiinflammatory; Dermatological; Immunosuppressive; Virucide; Antibacterial; Fungicide; Antimalarial; Respiratory-Gen.; Keratolytic; Anti-HIV; Antiasthmatic; Antiallergic; Neuroprotective; Vulnerary.

MECHANISM OF ACTION - Toll like receptor (TLR)8 agonist; Tumor necrosis factor (TNF) production inhibitor; Interleukin (IL)-12 production inhibitor. A combination (test) comprising 2-propylthiazolo(4,5-c)quinolin-4-amine (IRM) (3 µM) and 5'-TCGTCGAACGTTTCGAGATGAT-3' (CpG ODN M352) (10 µM) was prepared and tested for TLR8 agonistic activity using HEK 293 cells. Cell aliquots were

treated by (C1). As controls, some cell aliquots were incubated with 3  $\mu$ M of IRM only (positive control) and other cell aliquots were incubated with (CpG ODN M352) only (negative control). In all cases, the cells were incubated overnight at 37degreesC with 5% CO2 and 98% humidity. Each well of the plate was read on a L-max luminometer. The data was expressed as fold increase of luciferase induction in cell aliquots incubated with the indicated stimulant compared to the negative control. The fold increase for test/positive control/negative control was found to be approximately 104/approximately 39/approximately 0.5.

USE - For inducing at least one toll like receptor (TLR) 8-mediated biological activity (e.g. synthesis of a cytokine such as tumor necrosis factor (TNF) and interleukin (IL)-12, synthesis of a chemokine, synthesis of co-stimulatory markers, maturation of antigen-presenting cells and proliferation of B lymphocytes) in immune cells (e.g. peripheral blood mononuclear cells (PBMCs) and monocyte-derived dendritic cells) (claimed). The combination is used for treatment of cancer; lupus erythematosus; viral diseases; bacterial diseases; other infectious diseases such chlamydia; fungal diseases including aspergillosis, histoplasmosis, cryptococcal meningitis and parasitic diseases (including malaria, pneumocystis carinii pneumonia, leishmaniasis, cryptosporidiosis, toxoplasmosis and trypanosome infection); neoplastic diseases such as intraepithelial neoplasias, cervical dysplasia, actinic keratosis, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, melanoma, renal cell carcinoma, leukemia; TH2-mediated atopic diseases such as atopic dermatitis and eczema, eosinophilia, asthma, allergy, allergic rhinitis and Ommen's syndrome; autoimmune diseases such as systemic lupus erythematosus, thrombocythemia, multiple sclerosis, discoid lupus, alopecia areata; and diseases associated with wound repair such as inhibition of keloid formation and other types of scarring (e.g. enhancing wound healing, including chronic wounds). The combination can be used in the treatment of humans, rodents, dogs, cats, horses, pigs, sheep, goats, or cows.

ADVANTAGE - The combination can provide greater immunostimulatory activity than either component can provide alone i.e. can provide at least two-fold (preferably at least three-fold, especially at least five-fold) even greater increase in at least one toll like receptor (TLR) 8-mediated biological activity compared to that induced by a TLR8 agonist administered without the immunostimulatory oligonucleotide; can provide synergistic immunostimulatory activity; improves the efficacy of certain immunological treatments that involves a TLR8-mediated biological activity; enhances vaccine-induced TLR8-mediated biological activity to improve the efficacy of the vaccine - even to the point of enabling a vaccine previously considered ineffective to be considered effective; and can enable some immunological treatments to be clinically and/or commercially viable that previously had been considered clinically and/or commercially undesirable because of cost of a component of the treatment, availability of all components and/or the amount of a component (e.g. an antigen) previously considered necessary to generate an effective immune response also generated an undesirable level of side effects.

ACCESSION NUMBER: 2006-424284 [43] WPIDS  
DOC. NO. CPI: C2006-133823 [43]  
TITLE: Immunostimulatory combination for inducing toll  
like receptor 8-mediated  
biological activity e.g. synthesis of cytokine for  
treating e.g. cancer comprises toll  
like receptor 8 agonist in  
combination with immunostimulatory oligonucleotide  
DERWENT CLASS: B02; B03; C02  
INVENTOR: GORDEN K B; QIU X; WIGHTMAN P D  
PATENT ASSIGNEE: (MINN-C) 3M INNOVATIVE PROPERTIES CO  
COUNTRY COUNT: 111

PATENT INFO ABBR.:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2006063152	A2	20060615	(200643)*	EN	39	[9]

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2006063152	A2	WO 2005-US44448	20051208

PRIORITY APPLN. INFO: US 2004-634146P 20041208